Continuous flow synthesis of heterocyclic scaffolds

Design principles of multistep systems – A review

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Abstract

The synthesis of novel heterocycles is an essential task in small-molecule drug discovery. Continuous flow processing opens the way for a new paradigm in laboratory-scale synthesis as well as pharmaceutical manufacturing. Based on our experiences with the multistep synthesis of condensed benzothiazoles, we gathered some of the key design features in light of literature examples.

Introduction

The design and preparation of new heterocycles as scaffolds or building blocks for active pharmaceutical ingredients (APIs) is a challenging area in today's small-molecule drug discovery. Chemists seek new approaches and technologies that can be applied to produce novel structures, while keeping an eye on increasing the efficiency and productivity of chemical processes. The new "enabling technologies"[1,2], like flow chemistry[3,4], provide practical solution for the synthesis of heterocyclic compounds. The emerging trends and recent synthetic results indicate the growing importance of continuous flow manufacturing in academia as well as pharmaceutical industry[5–9]. These efforts are also pointing towards the realization of continuous technologies for API synthesis[10,11] in accordance with FDA's recommendations[12,13].

However, the application of flow methods demands a paradigm shift in synthetic mentality and a new knowledge base, which can mean a barrier for those, who are unfamiliar with it. Our

experience during the introduction of this technology to laboratory practice inspired us to compile this mini-review, to make flow chemistry more accessible. Here we discuss the problems and their solutions we faced during our research on the multistep synthesis of condensed benzothiazoles[14] (Fig. 1), in the light of recent literature references.

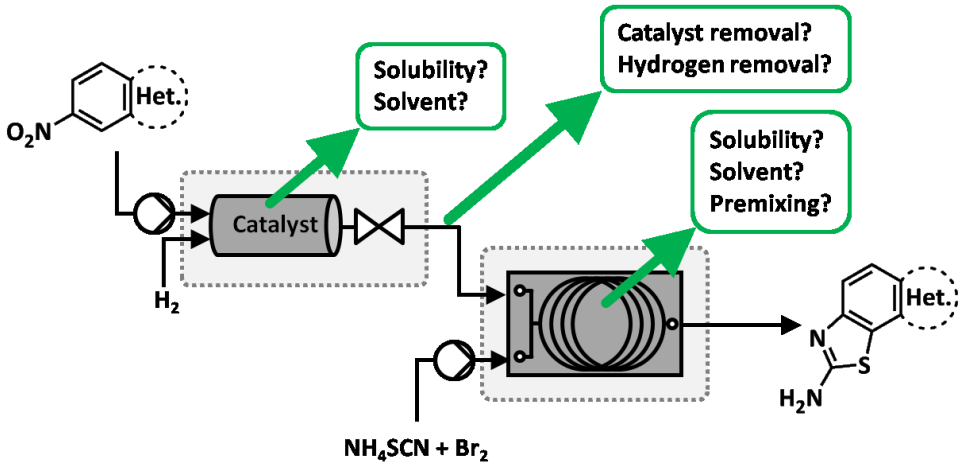

Fig. 1. Considerations for the proposed multistep continuous flow synthesis of condensed benzothiazoles.

Heterocyclic scaffolds in drug discovery

The development of new leads for APIs is largely based on the design and synthesis of new heterocycles. Applying them as building blocks, biological activity and physicochemical properties (like solubility, polarity and lipophilicity) of a given molecule can be modulated. In medicinal chemistry, the term “scaffold” is used for the core structure of a molecule, which is often a heterocyclic ring or ring system. In cases, when issues with these properties or the novelty of a specific compound series cannot be solved by modification of the side chains, the replacement of the central moiety (“scaffold hopping”) may become necessary, while keeping similar biological profile. Furthermore, the different chemical structure can lead to new patentable compound libraries[15–17].

Although a wide range of heterocycles are theoretically available[18,19], the obtainable number and variety thereof is limited by the parameter window, and convenience of the synthesis[20–22]. In the preparation of such compounds with increasing complexity, the classical laboratory-scale methods are often difficult. Multiple steps, use of hazardous reagents, high pressure or temperature are usually required. These circumstances can hinder the production of the desired structures in large numbers. Flow chemistry, as an "enabling technology" provides new opportunities to broaden the chemical space.

Design of the flow reactions

In our recent work[14] we have developed a multistep continuous flow approach for the synthesis of various tricyclic benzothiazoles (compounds **I-V**, Fig. 2).

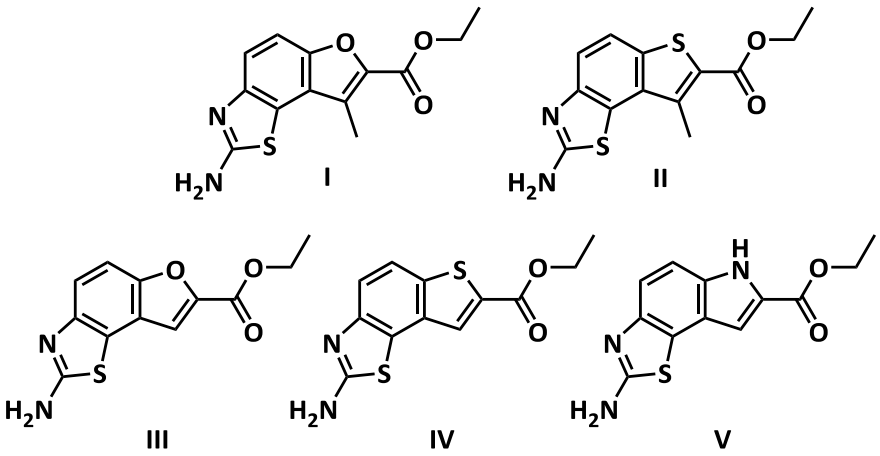

Fig. 2. The prepared tricyclic compounds.

We intended to obtain them in three steps: (1) the preparation of the corresponding bicyclic compounds bearing a nitro-group, (2) the reduction of the nitro-group and (3) the formation of thiazole ring. Possible issues with the selection of solvent, handling of insoluble and hazardous reagents and the implementation of hydrogenation were taken into account during the synthesis.

The choice of the **appropriate solvent** is a primary concern when designing continuous flow reactions. In the simplest case, a single solvent can be found which sufficiently dissolves all reagents, intermediates and products, and tolerates all reaction conditions. Even in this case, unexpected precipitation of transient species can occur, because the solubility of these compounds cannot be explored beforehand. Slight clogging can be flushed out if the system is carefully monitored. In our work, we found that *N*,*N*-dimethylformamide (DMF) could be applied in every step of the multistep protocol. The final step specifically required DMF, which could completely dissolve the products. This motivated us to switch the solvent of the hydrogenation step in order to simplify the whole sequence[14].

This solvent also proved to be the best option for the two-step syntheses of 5-(thiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one derivatives[23] and imidazo[1,2-a] heterocycles[24].

The high solubility of compounds and its compatibility with the integrated purification motivated the use of *N,N*-dimethylacetamide in the synthesis of 1,2,4-oxadiazole and 1,2,4-triazole libraries[25].

Dichloroethane was used in the telescoped synthesis of quinoxalines[26].

The **replacement of the insoluble reagents**, most often bases, by soluble alternatives is a common method to avoid clogging. *N,N*-diisopropylethylamine (DIPEA) is often used under flow conditions[24,25,27]. This base was successfully applied in our procedure for the synthesis of benzofurans and benzothiophenes, in order to replace potassium carbonate, which was used in

batch synthesis[14]. While this change did not affect the synthesis of benzothiophenes negatively, we found that this way the alkylation reaction yielded the intermediate in the case of benzofurans. In order to obtain the bicyclic products, we had to use a stronger base. Verkade's base ($P(CH_3NCH_2CH_2)_3N$) proved to be suitable in terms of the flow conditions, too[28] (Fig. 3).

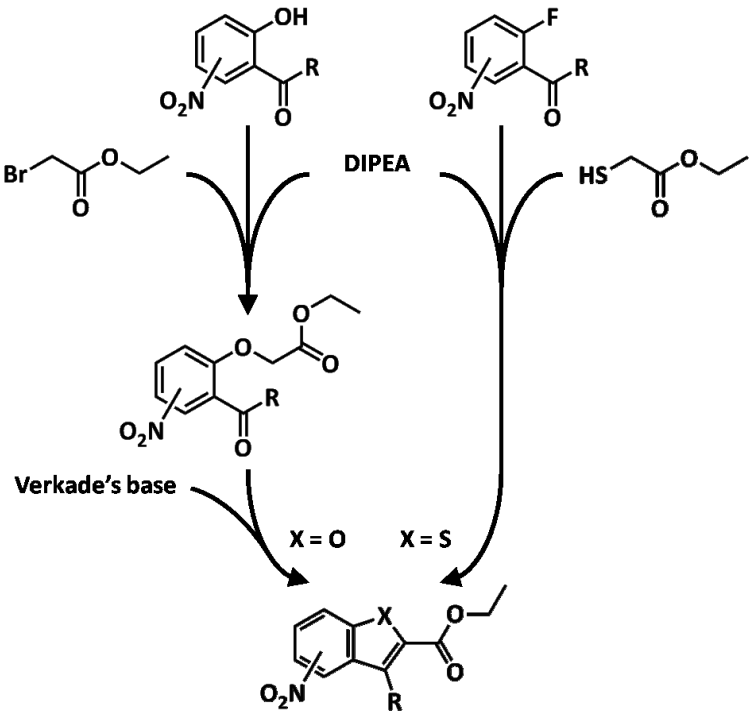

Fig. 3. The synthesis of benzofurans and benzothiophenes mediated by different bases.

Several examples are reported, in which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is used as soluble stronger base[29–31]. Solid supported alternatives of DBU[31] as well as other strong bases such as phosphazenes[29,32], were used in heterocyclic flow synthesis.

The **safe handling** of explosive or toxic reagents and the precise control of process conditions are two of the main benefits of flow chemistry that are getting more and more important both in laboratory environment and on industrial scale[11,33,34]. Due to the size of the microreactors, the actual reaction occurs only in small volume at a given time, which minimizes safety issues.

The handling of bromine in the continuous flow ring-closure reaction leading to tricycles[14] was safer than batch conditions, since the flow equipment can be regarded as a closed system, which prevents the escape of harmful vapours.

Hazardous reagents were handled or generated in-situ in the microreactor in syntheses of other heterocycles. Toxic alkyl nitrite and TMS azide reagents were safely used and the resulting explosive azides were transformed to stable triazole products in a two-step sequence[35]. Unstable diazoketones were synthesized and used without isolation for the preparation of wide range of quinoxalines[26].

Flow processes are also advantageous for **hydrogenations**. The benchtop hydrogenation modules enable the safe handling of both hydrogen and the heterogeneous catalysts, most

commonly loaded into packed bed reactors[36]. The separation of the catalyst from the reaction mixture is trivial with this setup, since it does not require additional filtration. In our work we utilized commercially available continuous flow hydrogenation equipment with preloaded Pd/C cartridges for nitro-reduction in the first step of our sequence. Due to the careful optimization[37], sufficiently clean product (without leaching of the catalyst) was obtainable in every case, which helped to avoid the otherwise problematic purification of the sensitive amines[14].

Several examples of selective ring saturation, late-stage modification and protecting group removal can be mentioned in this context, using flow hydrogenation[38–40]. Similar approach was applied for the hydrogenation of hydrazone during the three step synthesis leading to the intermediate of the API Atazanavir[41].

Incorporation of the reactions into a continuous flow system

One of the main goals of continuous flow processes is to perform multistep reactions in **telescoped** way. To achieve this, every single reaction parameter, chemical transformation and flow equipment should be taken into account. As the intermediates are not purified and isolated at the end of each step, all reaction steps have to be designed to be compatible with the whole sequence.

In the course of our synthesis[14], the aromatic amines prepared in the first steps proved to be unstable leading to decomposition products during purification. We realized at this point that the initially envisioned telescoped approach (Fig. 4) would show its benefits in this particular problem. This way, the outcome of the multistep system was better than the overall yield of the single steps.

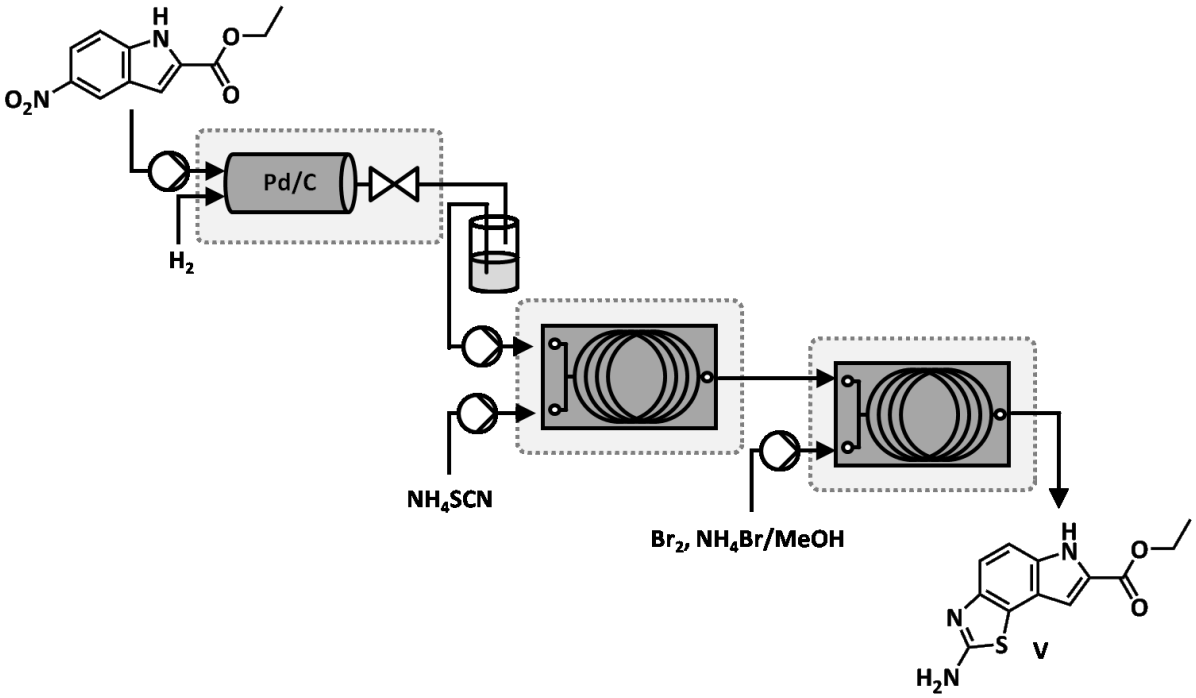

Fig. 4. The multistep continuous flow synthesis of compound **V**.

However, during investigation of the connected system we found, that utilization of the stream from the first step led to poorer results in the formation of the thiazole ring, compared to the same reaction conducted as an isolated step.

We assumed that in this case the lack of the **premixing** of the amines with ammonium thiocyanate, which happens in the storage flask in the single step procedure, hindered the following reaction with bromine. Increasing the mixing time by adding a coil reactor before the introduction of bromine, we could obtain higher overall yields. Although, this modification increased the **number of steps** (which contributes to complexity adversely), it was advantageous in context of the whole process. Similar observations on the importance of the mixing time, in terms of the overall yield and kinetics of the reaction were made in the continuous flow synthesis of 4,5-disubstituted oxazoles[32].

When connecting the separately optimised steps in our work, we had to remove the hydrogen used in the nitro-reduction, prior to the thiazole formation. The addition of a buffer vessel to the reaction stream was sufficient for **degassing**. The same solution was employed in the multistep flow synthesis of Rolipram[42], while other researchers tended to avoid the problem of gas separation and conduct hydrogenation as the last step[40,41].

Further implications

Besides the above mentioned advantages, the application of flow chemistry enables the **rapid optimization** of reactions and synthesis of **compound libraries** together with

automatization[43,44]. In our study the quick automated optimization[45,46] of conditions for each reactions was possible[14]. With the appropriate setup, small volume reaction mixtures can be handled fast and safely, which also lowers reagent consumption of the optimization process. New reactions can be discovered this way, for example, novel route to the core heterocycle of Efavirenz was enabled by extensive screening of conditions[47].

Several analogues and larger compound libraries can be prepared, thankful to the **variability** of such systems. Numerous examples show that this concept is viable using specific, carefully designed and optimised fluidic setups[23,29,32,35,48,49].

Conclusion

The application of flow chemistry has great perspectives in drug discovery. In order to take advantage of its benefits, chemists need to learn to design and build complex continuous flow systems. In this mini-review we have focused on the everyday challenges of laboratory-scale multistep flow synthesis. We aimed to present some of the design principles through our work in this field along with literature examples in order to help others with their own experiments in this field.

References

(1) Ley, S. V.; Baxendale, I. R. The Changing Face of Organic Synthesis. *Chim. Int. J. Chem.* **2008**, *62*, 162–168.

(2) O'Brien, M.; Denton, R.; Ley, S. Lesser-Known Enabling Technologies for Organic Synthesis. *Synthesis* **2011**, *2011*, 1157–1192.

(3) Wegner, J.; Ceylan, S.; Kirschning, A. Ten Key Issues in Modern Flow Chemistry. *Chem. Commun. (Camb).* **2011**, *47*, 4583–4592.

(4) McQuade, D. T.; Seeberger, P. H. Applying Flow Chemistry: Methods, Materials, and Multistep Synthesis. *J. Org. Chem.* **2013**, *78*, 6384–6389.

(5) Malet-Sanz, L.; Susanne, F. Continuous Flow Synthesis. A Pharma Perspective. *J. Med. Chem.* **2012**, *55*, 4062–4098.

(6) Baumann, M.; Baxendale, I. R.; Ley, S. V. The Flow Synthesis of Heterocycles for Natural Product and Medicinal Chemistry Applications. *Mol. Divers.* **2011**, *15*, 613–630.

(7) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology-A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chemie Int. Ed.* **2015**, *54*, 6688–6728.

(8) Kobayashi, S. Flow "Fine" Synthesis: High Yielding and Selective Organic Synthesis by Flow Methods. *Chem. - An Asian J.* **2016**, *11*, 425–436.

(9) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. On-Demand Continuous-Flow Production of Pharmaceuticals in a Compact, Reconfigurable System. *Science* **2016**, *352*, 61–67.

(10) Kirschneck, D. Manufacturing Efficiency by Modular Multipurpose Plants Combining Batch Flexibility with Continuous Flow Chemistry Performance. *Chim. Oggi-Chemistry Today* **2010**, *28*, 55–59.

(11) Gutmann, B.; Kappe, C. O. Forbidden Chemistries Go Flow in API Synthesis. *Chim. Oggi-Chemistry Today* **2015**, *33*, 18–25.

(12) Brennan, Z. FDA calls on manufacturers to begin switch from batch to continuous production http://www.in-pharmatechnologist.com/Processing/FDA-calls-on-manufacturers-to-begin-switch-from-batch-to-continuous-production (accessed May 23, 2016).

(13) Yu, L. Continuous Manufacturing Has a Strong Impact on Drug Quality http://blogs.fda.gov/fdavoice/index.php/2016/04/continuous-manufacturing-has-a-strong-impact-on-drug-quality/ (accessed May 23, 2016).

(14) Lövei, K.; Greiner, I.; Éles, J.; Szigetvári, Á.; Dékány, M.; Lévai, S.; Novák, Z.; Túrós, G. I. Multistep Continuous-Flow Synthesis of Condensed Benzothiazoles. *J. Flow Chem.* **2015**, *5*, 74–81.

(15) Gomtsyan, A. Heterocycles in Drugs and Drug Discovery. *Chem. Heterocycl. Compd.* **2012**, *48*, 7–10.

(16) Böhm, H.-J.; Flohr, A.; Stahl, M. Scaffold Hopping. *Drug Discov. Today Technol.* **2004**, *1*, 217–224.

(17) Brown, N.; Jacoby, E. On Scaffolds and Hopping in Medicinal Chemistry. *Mini-Reviews Med. Chem.* **2006**, *6*, 1217–1229.

(18) Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. Heteroaromatic Rings of the Future. *J. Med. Chem.* **2009**, *52*, 2952–2963.

(19) Reymond, J.-L.; Awale, M. Exploring Chemical Space for Drug Discovery Using the Chemical Universe Database. *ACS Chem. Neurosci.* **2012**, *3*, 649–657.

(20) Keserű, G. M.; Soós, T.; Kappe, C. O. Anthropogenic Reaction Parameters - the Missing Link between Chemical Intuition and the Available Chemical Space. *Chem. Soc. Rev.* **2014**, *43*, 5387–5399.

(21) Hann, M. M.; Keserü, G. M. Finding the Sweet Spot: The Role of Nature and Nurture in Medicinal Chemistry. *Nat. Rev. Drug Discov.* **2012**, *11*, 355–365.

(22) *Novel Process Windows*; Hessel, V.; Kralisch, D.; Kockmann, N., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2014.

(23) Pagano, N.; Herath, A.; Cosford, N. N. D. P. Automated Process for a Sequential Heterocycle/Multicomponent Reaction: Multistep Continuous Flow Synthesis of 5-(Thiazol-2-Yl)-3, 4-Dihydropyrimidin-2 (1H)-Ones. *J. Flow Chem.* **2012**, *2*, 28–31.

(24) Herath, A.; Dahl, R.; Cosford, N. D. P. Fully Automated Continuous Flow Synthesis of Highly Functionalized imidazo[1,2-a] Heterocycles. *Org. Lett.* **2010**, *12*, 412–415.

(25) Bogdan, A. R.; Wang, Y. A High-Throughput Synthesis of 1,2,4-Oxadiazole and 1,2,4-Triazole Libraries in a Continuous Flow Reactor. *RSC Adv.* **2015**, *5*, 79264–79269.

(26) Martin, L. J.; Marzinzik, A. L.; Ley, S. V; Baxendale, I. R. Safe and Reliable Synthesis of Diazoketones and Quinoxalines in a Continuous Flow Reactor. *Org. Lett.* **2011**, *13*, 320–323.

(27) Hodgkinson, J. T.; Galloway, W. R. J. D.; Saraf, S.; Baxendale, I. R.; Ley, S. V; Ladlow, M.; Welch, M.; Spring, D. R. Microwave and Flow Syntheses of Pseudomonas Quinolone Signal (PQS) and Analogues. *Org. Biomol. Chem.* **2011**, *9*, 57–61.

(28) D'Sa, B. A.; Kisanga, P.; Verkade, J. G. P(MeNCH2CH2)3N: An Efficient Catalyst for the Synthesis of Substituted Ethyl Benzofuran-2-Carboxylates. *Synlett* **2001**, *2001*, 670–672.

(29) Baxendale, I. R.; Ley, S. V; Smith, C. D.; Tamborini, L.; Voica, A.-F. A Bifurcated Pathway to Thiazoles and Imidazoles Using a Modular Flow Microreactor. *J. Comb. Chem.* **2008**, *10*, 851–857.

(30) Schwalbe, T.; Kadzimirsz, D.; Jas, G. Synthesis of a Library of Ciprofloxacin Analogues By Means of Sequential Organic Synthesis in Microreactors. *QSAR Comb. Sci.* **2005**, *24*,

758–768.

(31) Baxendale, I.; Buckle, C.; Ley, S.; Tamborini, L. A Base-Catalysed One-Pot Three-Component Coupling Reaction Leading to Nitrosubstituted Pyrroles. *Synthesis* **2009**, *2009*, 1485–1493.

(32) Baumann, M.; Baxendale, I. R.; Ley, S. V; Smith, C. D.; Tranmer, G. K. Fully Automated Continuous Flow Synthesis of 4,5-Disubstituted Oxazoles. *Org. Lett.* **2006**, *8*, 5231–5234.

(33) Brocklehurst, C. E.; La Vecchia, L.; Lehmann, H. Enabling Technologies in Pharmaceutical Industry Scale-up of Hazardous Reactions in Continuous Flow. *Chim. Oggi-Chemistry Today* **2014**, *32*, 30–35.

(34) Müller, S. T. R.; Murat, A.; Hellier, P.; Wirth, T. Safe Handling of Diazo Reagents through Inline Analytics and Flow Chemistry. *Chim. Oggi-Chemistry Today* **2015**, *33*, 74–78.

(35) Smith, C. J.; Nikbin, N.; Ley, S. V; Lange, H.; Baxendale, I. R. A Fully Automated, Multistep Flow Synthesis of 5-Amino-4-Cyano-1,2,3-Triazoles. *Org. Biomol. Chem.* **2011**, *9*, 1938–1947.

(36) Jones, R. V; Godorhazy, L.; Varga, N.; Szalay, D.; Urge, L.; Darvas, F. Continuous-Flow High Pressure Hydrogenation Reactor for Optimization and High-Throughput Synthesis. *J. Comb. Chem.* **2006**, *8*, 110–116.

(37) Bryan, M. C.; Wernick, D.; Hein, C. D.; Petersen, J. V; Eschelbach, J. W.; Doherty, E. M. Evaluation of a Commercial Packed Bed Flow Hydrogenator for Reaction Screening, Optimization, and Synthesis. *Beilstein J. Org. Chem.* **2011**, *7*, 1141–1149.

(38) Irfan, M.; Glasnov, T. N.; Kappe, C. O. Heterogeneous Catalytic Hydrogenation Reactions in Continuous-Flow Reactors. *ChemSusChem* **2011**, *4*, 300–316.

(39) Hizartzidis, L.; Cossar, P. J.; Robertson, M. J.; Simone, M. I.; Young, K. A.; McCluskey, A.; Gordon, C. P. Expanding the Utility of Flow Hydrogenation – a Robust Protocol Restricting Hydrodehalogenation. *RSC Adv.* **2014**, *4*, 56743–56748.

(40) Cossar, P. J.; Hizartzidis, L.; Simone, M. I.; McCluskey, A.; Gordon, C. P. The Expanding Utility of Continuous Flow Hydrogenation. *Org. Biomol. Chem.* **2015**, *13*, 7119–7130.

(41) Dalla-Vechia, L.; Reichart, B.; Glasnov, T.; Miranda, L. S. M.; Kappe, C. O.; de Souza, R. O. M. A. A Three Step Continuous Flow Synthesis of the Biaryl Unit of the HIV Protease Inhibitor Atazanavir. *Org. Biomol. Chem.* **2013**, *11*, 6806–6813.

(42) Tsubogo, T.; Oyamada, H.; Kobayashi, S. Multistep Continuous-Flow Synthesis of (R)- and (S)-Rolipram Using Heterogeneous Catalysts. *Nature* **2015**, *520*, 329–332.

(43) Ley, S. V.; Fitzpatrick, D. E.; Ingham, R. J.; Myers, R. M. Organic Synthesis: March of the Machines. *Angew. Chemie Int. Ed.* **2015**, *54*, 3449–3464.

(44) Fitzpatrick, D. E.; Battilocchio, C.; Ley, S. V. Enabling Technologies for the Future of Chemical Synthesis. *ACS Cent. Sci.* **2016**, *2*, 131–138.

(45) Reichart, B.; Tekautz, G.; Kappe, C. O. Continuous Flow Synthesis of N -Alkyl Chlorides

in a High-Temperature Microreactor Environment. *Org. Process Res. Dev.* **2013**, *17*, 152–157.

(46) Becker, R.; Koch, K.; Nieuwland, P. J.; Rutjes, F. P. J. T. Flow Chemistry Today: Practical Approaches for Optimisation and Scale-Up. *Chim. Oggi-Chemistry Today* **2012**, *30*, 6–8.

(47) Correia, C. A.; Gilmore, K.; McQuade, D. T.; Seeberger, P. H. A Concise Flow Synthesis of Efavirenz. *Angew. Chemie Int. Ed.* **2015**, *54*, 4945–4948.

(48) Tricotet, T.; O'Shea, D. F. Automated Generation and Reactions of 3-Hydroxymethylindoles in Continuous-Flow Microreactors. *Chem. Eur. J.* **2010**, *16*, 6678–6686.

(49) Guetzoyan, L.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. Flow Chemistry Synthesis of Zolpidem, Alpidem and Other GABAA Agonists and Their Biological Evaluation through the Use of in-Line Frontal Affinity Chromatography. *Chem. Sci.* **2013**, *4*, 764–769.